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(54) Compositions for treating viral skin diseases

(57) Topical pharmaceutical compositions, e.g. in gel or ointment form, comprise a keratolytic agent and a non-specific nucleoside analogue e.g. idoxuridine. The compositions may be used to treat e.g. herpetic infections and warts. The keratolytic agent is especially urea or salicylic acid.

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The claims were filed later than the filing date within the period prescribed by Rule 25(1) of the Patents Rules 1982.

SPECIFICATION

Chemical compositions

This invention relates to chemical compositions and in particular to pharmaceutical compositions for topical application containing an anti-viral nucleoside analogue.

Anti-viral nucleoside analogues, such as idoxuridine, acyclovir and bromvinyldeoxuridine (BVDU), act by inhibiting viral replication of DNA viruses, for example herpes simplex and herpes zoster. These anti-viral agents are in fact pro-drugs which are activated by the thymidine kinase enzymes which are present in affected cells. However, these agents divide into two classes. One class, which includes for example acyclovir and BVDU, is of pro-drugs which are activated specifically by the thymidine kinases produced in the virally infected cells. The second class, which includes for example idoxuridine, is of pro-drugs for which the thymidine kinase activator need not be that produced in the virally infected cells. The pro-drugs of the first and second classes are referred to hereinafter as specific and non-specific nucleoside analogues respectively.

Anti-viral nucleoside analogues have been widely used in the topical treatment of skin lesions of viral origin, such as for example herpes simplex and herpes zoster. The use of such agents in the treatment of anogenital warts (condylomata accuminata) has also been suggested. However, these agents have been found to be ineffective in the treatment of certain other viral skin infections, and particularly in the treatment of common viral warts (verucca vulgaris) where activation of the pro-drug does not appear to occur.

It is an object of the present invention to provide a pharmaceutical composition comprising as an active agent a non-specific anti-viral nucleoside analogue, which composition is suitable for the treatment of viral skin infections, including for example common viral warts.

According to one aspect of the present invention there is thus provided a topical pharmaceutical composition comprising in combination a non-specific anti-viral nucleoside analogue and a keratolytic agent.

The compositions of the present invention may contain a basic keratolytic agent (such as urea) or an acidic keratolytic agent (such as salicylic acid). The amount of the keratolytic agent present in the compositions of the invention will suitably be sufficient to cause thymidine kinases to be released in or around the affected tissue; thus the precise amount clearly depends on the nature of the keratolytic agent used but generally be up to about 15% by weight. The non-specific anti-viral nucleoside analogue in the compositions of the present invention is preferably idoxuridine. Where a poorly water soluble nucleoside analogue such as idoxuridine is used, the compositions of the present invention should also contain a material in which the nucleoside analogue is soluble and which can serve as a skin penetration agent. Suitable solvents/skin penetration agents include dimethylsulphoxide (DMSO) and dimethylsulphacetamide, but DMSO is generally preferred despite its known side effects. The level of the non-specific nucleoside analogue in the compositions of the invention will generally depend upon the condition which is to be treated using those compositions. However, if idoxuridine is used, concentrations may conveniently be in the range of 0.1–40%, and will preferably by from 2–10%, especially about 5% by weight. The solvent/skin penetration agent, if present, will be used at a concentration at least sufficient to maintain the nucleoside analogue in solution. In the case of a gel composition, for example, a DMSO content of 65% by weight has been found sufficient to support a 5% by weight concentration of idoxuridine.

The viral replication rate in common warts is very slow relative for example to herpes viruses and the compositions of the present invention are advantageously in the form of ointments or gels so as to provide, for each application of the composition, a more prolonged exposure of the infected cells to the anti-viral agent than would be achievable with for example a solution.

Various ointment or gel matrices for anti- viral agents are known, such as for example polyethylene glycol, petroleum jelly/lanolin and plant-derived gels; however, in the compositions of the present invention, aqueous carbomer gels have been found to be particularly suitable.

The compositions according to the invention in gel form preferably comprise a gelling agent in which the non-specific nucleoside analogue is substantially insoluble and a solvent/skin penetration agent (e.g. DMSO) in which the non-specific nucleoside analogue is soluble. In this respect, the gelling agent is preferably a carbomer, hydr xypropylcellulose (e.g. Kluc l HF available from Hercules Incorporated) or an acrylic polymer such as the alkali-soluble acrylic polymer emulsion available from Chesham Chemicals Limit d under the trade name Acrysol ICS–1. If Acrysol ICS–1 is used, it is thickened by the additi n of a base such as those describ d in the following paragraph.

Where carb mers are used as gel forming agents in the compositions f th present invention, they require neutralisati n with a physiologically acceptabl base, for example an alkali metal hydroxide or an amine, and the resultant gels are non theless somewhat acid-sensitive. Suitable carbomers include those available from The BF Goodrich Company under the trade name Carbopol, and particularly water-soluble carbomers having molecular weights in the range one to five

million, e.g. Carbopol 934P, Carbopol 940 and Carbopol 941. In such carbomer-containing compositions, the use according to the present invention of basic keratolytic agents actually serves the further function of enhancing the stability of the gel matrix. Where a basic keratolytic agent is used, it will conveniently be present in the compositions of the present invention at from about 5–15% by weight, preferably 8–12% and especially about 10% by weight.

The compositions of the present invention may contain further optional components such as for example buffers, stabilizers, bulking agents and preservative agents. However, carbomer gel preparations produced according to the present invention have been found to be stable even without the addition of any preservative agents.

Where the compositions of the invention contain polyethylene glycol, for example as a gelling agent or as the bulking agent to bring compositions based on other gelling agents to the desired overall concentration of non-specific nucleoside analogue, liquid macrogols, e.g. Macrogol 300 and Macrogol 400 may conveniently be used. Macrogols are available from Union Carbide under the trade name Carbowax.

The compositions of the present invention may be used in the treatment of viral skin infections such as for example, common warts (verruca vulgaris), herpes simplex, herpes zoster and anogenital warts (condylomata accuminata). Treatment with the compositions of the invention would generally involve the topical application of the compositions to the affected area, generally about two to four times daily.

Thus in a further aspect, the present invention provides the use of a non-specific anti-viral nucleoside analogues and keratolytic agents for the manufacture of a therapeutic agent for the treatment of verucca vulgaris, condylomata accuminata, or herpetic infections such as herpes simplex or herpes zoster.

In further aspect, the present invention provides a method of treatment of verucca vulgaris, which method comprises the topical application to the wart of a non-specific anti-viral nuceloside analogue in combination with a keratolytic agent, preferably by the topical application of a composition according to the present invention.

While it is not confirmed, it is believed that the compositions of the present invention act by virtue of a combination of the effects of the keratolytic agent and the non-specific anti-viral nucleoside analogue. Thus in the treatment of verucca vulgaris, the keratolytic agent induces release of thymidine kinases from cells in or around the wart and thereby activates the non-specific anti-viral nucleoside analogue. In the absence of the keratolytic agent, the wart tissue appears to contain insufficient thymidine kinases to activate either non-specific or specific anti-viral nucleoside analogues.

The present invention is further illustrated by the following non-limiting Examples:

Example 1

A gel formulation is prepared having the following composition:

Iodoxuridine	5% by weight
Urea	10% by weight
Carbopol 934P	1% by weight
Dimethylsulphoxide	65% by weight
Triethanolamine – qs to pH 6.8	(approx. 0.15 ml)
Distilled water *ad*	100% by weight

Preparation

A concentrated solution of idoxuridine (40g) in dimethylsulphoxide (65g) is prepared. A concentrated dispersion of Carbopol 934P (10g – available from Goodrich) in distilled water (200g) is prepared and 21g of the dispersion is mixed with 57.5g of DMSO and then to this are added 12.5g of the concentrated solution of idoxuridine in DMSO. The urea (10g) is added and the pH is then adjusted to 6.8 with the addition of triethanolamine (10% in water). The gel is made up to 100% with distilled water and then packaged, for example by filling into tubes.

The gel produced is satisfactorily stable: no change in physical appearance or consistency has been observed on storage at ambient temperature and the gel has passed the BP test for preservative efficiency without requiring any addition of preservative agents.

Example 2

A gel formulation is prepared and packaged analagously to that described in Example 1. The gel has the following composition:

Idoxuridine		5% by weight
Urea		10% by weight
Carbopol 934P		1% by weight
Dimethylsulphoxide		65% by weight
Macrogol 400		10% by weight
Triethanolamine – qs to pH 6.8		
Distilled water	*ad*	100% by weight

Example 3

A gel formulation comprising Klucel HF as a gelling agent and Macrogol 300 as a bulking agent is prepared and packaged analogously to that described in Example 1. The gel formulation is clear, has good viscosity and has the following composition:

Idoxuridine		5% by weight
Urea		10% by weight
Klucel HF		3.5% by weight
Dimethylsulphoxide		65% by weight
Macrogol 300		10.5% by weight
Distilled water	*ad*	100% by weight

Example 4

A clear gel compositon comprising salicylic acid as the keratolytic agent is prepared with the following composition:

Idoxuridine		5% by weight
Salicylic acid		2% by weight
Klucel HF		2.5% by weight
Dimethylsulphoxide		65% by weight
Macrogol 300		18% by weight
Distilled water	*ad*	100% by weight

CLAIMS

1. A topical pharmaceutical composition comprising in combination a non-specific anti-viral nucleoside analogue and a keratolytic agent.

2. A composition as claimed in claim 1 wherein said nucleoside analogue is idoxuridine, said composition further containing a skin penetration agent in which idoxuridine is soluble.

3. A composition as claimed in claim 2 wherein said skin penetration agent comprises dimethylsulphoxide.

4. A composition as claimed in claim 3 containing about 65% by weight of dimethylsulphoxide.

5. A composition as claimed in any one of claims 2 to 4 containing from 0.1% to 40% by weight of idoxuridine.

6. A composition as claimed in claim 5 containing from 2 to 10% by weight of idoxuridine.

7. A composition as claimed in claim 5 containing about 5% by weight of idoxuridine.

8. A composition as claimed in any one of the preceding claims containing up to 15% by weight of said keratolytic agent.

9. A composition as claimed in any one of the preceding claims wherein said keratolytic agent is urea or salicylic acid.

10. A composition as claimed in any one of the preceding claims in gel or ointment form.

11. A composition as claimed in claim 10 in gel form comprising as a gelling agent at least one of the following: a carbomer neutralized with a physiologically acceptable base; hydroxypropyl cellulose; an acrylic polymer; and a polyethylene glycol.

12. A composition as claimed in claim 11 comprising as a gelling agent a neutralised water-soluble carbomer having a mol cular weight in the range of 10^6 to 5×10^6.

13. A composition as claim d in claim 12 containing from 5 t 15% by weight f a basic kerat lytic agent.

14. A composition as claimed in any ne f claims 11 to 13 further comprising a bulking agent s lected from polyethylene glycols and liquid macrogols.

15. A composition as claimed in any ne f claims 11 to 14 comprising idoxuridine, urea dimethylsulphoxide and a neutralized carbomer gelling agent.

16. A topical composition as claimed in any one of claims 1 to 15 substantially as hereinbe-

fore described with reference t the Examples.

17. The use of a non-specific anti-viral nucleoside analogue and a keratolytic agent for the manufacture of a therapeutic agent for the treatment of viral skin infection.

18. Use as claimed in claim 17 of idoxuridine and urea or salicylic acid for the manufacture of a therapeutic agent for the treatment of herpetic infections.

19. Use as claimed in claim 17 of idoxuridine and urea or salicylic acid for the manufacture of a therapeutic agent for the treatment of common warts.

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